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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,147	MALISZEWSKI ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/2/03;10/7/02*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *8-24 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/6/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-30 are pending.

2. Applicant's election without traverse of Group I, claims 1-7 and 25-29, drawn to a polypeptide comprising a soluble CD39 polypeptide and a composition thereof that read on the species of soluble CD39 polypeptide of claim 7 having the sequence of amino acids 21-463 of SEQ ID NO: 30, filed 7/2/03, is acknowledged.

3. Claims 8-24 and 30 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-7 and 25-29, drawn to a polypeptide comprising a soluble CD39 polypeptide and a composition thereof that read on the species of soluble CD39 polypeptide of claim 7 having the sequence of amino acids 21-463 of SEQ ID NO: 30, are being acted upon in this Office Action.

5. Claims 25-26 and 29 are objected to because said claims depend from non-elected invention.

6. The disclosure is objected to under 37 CFR 1.821(d) because SEQ ID NO: is required on page 13, line 35-36.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-7 and 25-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a soluble human CD39 polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 26, 27, 28, 29, 30 and 31, or a soluble human CD39 fusion polypeptide comprising a leader containing sequence consisting of the amino acid sequence selected from the group consisting of a human IL-2 polypeptide of SEQ ID NO: 9, N-terminal amino acid sequence of human CD39L-1 consisting of Met 1 to Ser37 of SEQ ID NO: 31 or Ala residue fused to a human CD39 consisting of the amino acid sequence

selected from the group consisting of amino acids 21-463 of SEQ ID NO: 30, Thr 38 to Thr 476 of SEQ ID NO: 2, and 49 to 487 of SEQ ID NO: 26, **does not** reasonably provide enablement for

(1) Any polypeptide having the structure of X-Y wherein X is *any* "heterologous peptides capable of adopting a stable secondary structure" and Y is any soluble CD39 polypeptide selected from the group consisting of (a) any polypeptide having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2), (b) any "fragments" of an polypeptide having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein said fragments have apyrase activity, and (c) any "variants" of any polypeptide having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2), (b) any fragment of an polypeptide having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein said fragments have apyrase activity, *any* polypeptide "having" a sequence consisting of amino acids 38-476 or 39-476 of SEQ ID NO: 2; any variant polypeptides that are at least 70%, 80%, 90%, 95%, 98%, or 99% identical in amino acid sequence to amino acids 36 to 478 of SEQ ID NO: 2 wherein said variant polypeptides have apyrase activity, any variant polypeptides that are at least 70%, 80%, 90%, 95%, 98%, or 99% identical in amino acid sequence to any fragment of SEQ ID NO: 2 wherein said variant polypeptides have apyrase activity;

(2) Any polypeptide having the structure of A-B-Y wherein A is any 0-20 amino acids from the amino terminal portion of any mature IL-2, B is any linker of 0-15 amino acids and Y is any soluble CD39 polypeptide, any soluble CD39 polypeptide such as (a) "polypeptides" having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein the amino terminus is selected from the group consisting of amino acids 36-44, and carboxyl terminus is selected from the group consisting of 471-478; (b) any "fragments of polypeptides" having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein the amino terminus is selected from the group consisting of amino acids 36-44, and carboxyl terminus is selected from the group consisting of 471-478 wherein said fragments have apyrase activity, and any variants of "polypeptides" having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein the amino terminus is selected from the group consisting of amino acids 36-44, and carboxyl terminus is selected from the group consisting of 471-478; (c) any "fragments of polypeptides" having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein the amino terminus is selected from the group consisting of amino acids 36-44, and carboxyl terminus is selected from the group consisting of 471-478 wherein said variants have apyrase activity;

(3) Any soluble CD39 polypeptide "comprising" a sequence selected from the group consisting of: (a) amino acids 25-464 of SEQ ID NO: 27; amino acids 25-464 of SEQ ID NO: 28; amino acids 27-473 of SEQ ID NO: 29, amino acids 21-476 of SEQ ID NO: 3; amino acids 21-476 of SEQ ID NO: 4; or amino acids 21-463 of SEQ ID NO: 30, (b) any fusion polypeptides "comprising" amino acids 25-464 of SEQ ID NO: 27; amino acids 25-464 of SEQ ID NO: 28; amino acids 27-473 of SEQ ID NO: 29, amino acids 21-476 of SEQ ID NO: 3; amino acids 21-476 of SEQ ID NO: 4; or amino acids 21-463 of SEQ ID NO: 30 wherein said fusion polypeptides have apapyrase activity;

(4) any fusion polypeptides "having" an amino acid sequence selected from the group consisting of amino acids 25-464 of SEQ ID NO: 27; amino acids 25-464 of SEQ ID NO: 28; amino acids 27-473 of SEQ ID NO: 29, amino acids 21-476 of SEQ ID NO: 3; amino acids 21-476 of SEQ ID NO: 4; or amino acids 21-463 of SEQ ID NO: 30;

(5) any polypeptide mentioned above produced by a process comprising culturing a recombinant cell such as CHO cell that has been adapted to grow in suspension and in the absence of serum comprising nucleic acid encoding any polypeptide as set forth in claim 1;

(6) any composition comprising a pharmaceutically acceptable carrier and any polypeptide mentioned above for treating any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only soluble human CD39 comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 26, 27, 28, 29, 30 and 31, or a soluble human CD39 fusion polypeptide comprising a leader containing sequence consisting of the amino acid sequence selected from the group consisting of a human IL-2 polypeptide of SEQ ID NO: 9, N-terminal amino acid sequence of human CD39L-1 consisting of Met 1 to Ser37 of

SEQ ID NO: 31 or Ala residue fused to a human CD39 consisting of the amino acid sequence selected from the group consisting of amino acids 21-463 of SEQ ID NO: 30, Thr 38 to Thr 476 of SEQ ID NO: 2, and 49 to 487 of SEQ ID NO: 26. The specification on page 10 discloses that CD39 polypeptides comprise one to ten deletions, insertions, or substitutions of amino acid residues, when compared to a native CD39 sequence. Variants of CD39 include polypeptides that are naturally occurring such as allelic forms, spliced forms, as well as that have been modifying in the amino acid sequence of a CD39 polypeptide or polynucleotide such as polypeptides are at least about 70%, 80%, 90%, 95%, 98% and 99% identical to the native CD39 of SEQ ID NO: 2.

However, the specification does not teach how to make any and all CD39 polypeptide mentioned above because there is insufficient guidance as to the structure of any CD39 polypeptide such as the ones recited in claims 1-7 without the amino acid sequence. There is insufficient guidance as to the structure of the "heterologous peptide capable of adopting a stable secondary structure" in claim 1. In addition, the term "having" is open-ended. It expands the soluble CD39 such as polypeptide as set forth in claim 1(a), and any "fragments" thereof as set forth in claim 1(b) to include additional amino acids at either or both ends. There is in a lack of guidance as to which amino acids within the full length CD39 polypeptide to be deleted, added or modified such that the resulting soluble CD39 polypeptide and variants thereof maintains its structure and biological activity. There is also a lack of guidance as to which amino acids within which "fragments" of 36 to 478 of SEQ ID NO: 2 to be deleted, added or modified such that the resulting soluble CD39 polypeptide fragment and variants thereof maintains its structure and apyrase activity. Further, the term "at least 70, 80, 90, 95, 98, 99 %" identical in amino acid sequence to a fragment of amino acids 36 to 478 of SEQ ID NO: 2 is ambiguous because the size of the fragment is unknown in claim 2. Even if the soluble CD39 polypeptide is limited to amino acids 36 to 478 of SEQ ID NO: 2, a polypeptide having a sequence "at least 70%, 80%, 90%, 95%, 98% and 99% identical means 30%, 20%, 10%, 5%, 2% and 1% differences, respectively. In other words, the soluble CD39 polypeptide is equivalent to having at least 133, 88, 44, 22, 8 and 4 amino acids difference relative to 36 to 478 of SEQ ID NO: 2. There is a lack of guidance as to which 133, 88, 44, 22, 8 and 4 amino acids relative to 36 to 478 of SEQ ID NO: 2 to be modified such as addition, deletion, substitution such that the resulting polypeptide maintains its structure and function. The use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be

defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Because applicants have not disclosed the specific condition used to score sequence identity while using any computer program mentioned above, it is unpredictable which amino acid sequences will have 70% identity to the claimed sequences and still retain the activities. Thus it would require undue experimentation for one of skill in the art to identify amino acid sequences that not only are 70% identical to the claimed sequences but also have functional activity.

It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Mikayama *et al.*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Attwood *et al.* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document). Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). Grinthal et al teach that a single His to Gly substitution at position 59 in CD39 changes substrate specificity such as an apyrase to an adenosine diphosphatase (ADPase) in a manner that depends on intact associations of both transmembrane domains with the membrane (see abstract, in particular). Given the unlimited number of CD39 polypeptide, fragments, variants thereof, there is insufficient in vivo working example demonstrating any polypeptide having the structure of X-Y has apyrase activity, much less for treating any disease.

With regard to claim 4, the same reasons stated above apply to claim 4 in terms of "fragments" and "variants". Further, there is insufficient guidance as to the structure and function of "A" such as which 0-20 amino acids from the terminal portion of mature IL-2, "B" such as which linker peptide of 0-15 amino acids and Y such as soluble CD39 polypeptide without the amino acid sequence, let alone multiple "fragments" and "variants". The specification does not disclose any combination of amino terminus such as amino acids 36-44 and carboxyl terminus such as 471-478 of SEQ ID NO: 2 for the soluble CD39 polypeptide.

With regard to claims 5-7, the term "comprising" or "having" is open-ended. It expands the soluble CD39 polypeptide or fusion polypeptide to include additional amino acids at either or both ends in addition to the stated amino acids such as amino acids 25-464 of SEQ ID NO: 27; amino acids 25-464 of SEQ ID NO: 28; amino acids 27-473 of SEQ ID NO: 29, amino acids 21-476 of SEQ ID NO: 3; amino acids 21-476 of SEQ ID NO: 4; or amino acids 21-463 of SEQ ID NO: 30. There is inadequate guidance as to which amino acids to be added or which protein said sequences fused to (claim 5b) and whether the resulting soluble CD39 polypeptide or fusion polypeptide maintains its structure and function, in turn, would be useful for inhibiting platelet activation and treating disease such as stroke, or inhibiting angiogenesis. Given the unlimited number of CD39 polypeptide, fragments, variants thereof, it is unpredictable which polypeptide having the structure of X-Y or A-B-Y has apyrase activity, much less for treating any disease. Since the structure of the polypeptides mentioned above are not enabled, it follows that the polypeptide made by the process of culturing recombinant host cell such as COS cells is not enabled. It also follows that any composition comprising any undisclosed polypeptide mentioned above and a pharmaceutically acceptable carrier are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 1-7 and 25-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) Any polypeptide having the structure of X-Y wherein X is *any* "heterologous peptides capable of adopting a stable secondary structure" and Y is any soluble CD39 polypeptide selected from the group consisting of (a) any polypeptide having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2), (b) any "fragments" of an polypeptide having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein said fragments have apyrase activity, and (c) any "variants" of any polypeptide having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2), (b) any fragment of an polypeptide having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein said fragments have apyrase activity, *any* polypeptide "having" a sequence consisting of amino acids 38-476 or 39-476 of SEQ ID NO: 2; any variant polypeptides that are at least 70%, 80%, 90%, 95%, 98%, or 99% identical in amino acid sequence to amino acids 36 to 478 of SEQ ID NO: 2 wherein said variant polypeptides have apyrase activity, any variant polypeptides that are at least 70%, 80%, 90%, 95%, 98%, or 99% identical in amino acid sequence to any fragment of SEQ ID NO: 2 wherein said variant polypeptides have apyrase activity;

(2) Any polypeptide having the structure of A-B-Y wherein A is any 0-20 amino acids from the amino terminal portion of any mature IL-2, B is any linker of 0-15 amino acids and Y is any soluble CD39 polypeptide, any soluble CD39 polypeptide such as (a) "polypeptides" having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein the amino terminus is selected from the group consisting of amino acids 36-44, and carboxyl terminus is selected from the group consisting of 471-478; (b) any "fragments of polypeptides" having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein the amino terminus is selected from the group consisting of amino acids 36-44, and carboxyl terminus is selected from the group consisting of 471-478 wherein said fragments have apyrase activity, and any variants of "polypeptides" having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein the amino terminus is selected from the group consisting of amino acids 36-44, and carboxyl terminus is selected from the group consisting of 471-478; (c) any "fragments of polypeptides" having an amino acid sequence as set forth in Figure 1 (SEQ ID NO: 2) wherein the amino

terminus is selected from the group consisting of amino acids 36-44, and carboxyl terminus is selected from the group consisting of 471-478 wherein said variants have apyrase activity;

(3) Any soluble CD39 polypeptide "comprising" a sequence selected from the group consisting of: (a) amino acids 25-464 of SEQ ID NO: 27; amino acids 25-464 of SEQ ID NO: 28; amino acids 27-473 of SEQ ID NO: 29, amino acids 21-476 of SEQ ID NO: 3; amino acids 21-476 of SEQ ID NO: 4; or amino acids 21-463 of SEQ ID NO: 30, (b) any fusion polypeptides "comprising" amino acids 25-464 of SEQ ID NO: 27; amino acids 25-464 of SEQ ID NO: 28; amino acids 27-473 of SEQ ID NO: 29, amino acids 21-476 of SEQ ID NO: 3; amino acids 21-476 of SEQ ID NO: 4; or amino acids 21-463 of SEQ ID NO: 30 wherein said fusion polypeptides have apapyrase activity;

(4) any fusion polypeptides "having" an amino acid sequence selected from the group consisting of amino acids 25-464 of SEQ ID NO: 27; amino acids 25-464 of SEQ ID NO: 28; amino acids 27-473 of SEQ ID NO: 29, amino acids 21-476 of SEQ ID NO: 3; amino acids 21-476 of SEQ ID NO: 4; or amino acids 21-463 of SEQ ID NO: 30;

(5) any polypeptide mentioned above produced by a process comprising culturing a recombinant cell such as CHO cell that has been adapted to grow in suspension and in the absence of serum comprising nucleic acid encoding any polypeptide as set forth in claim 1;

(6) any composition comprising a pharmaceutically acceptable carrier and any polypeptide mentioned above.

The specification discloses only soluble human CD39 comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 26, 27, 28, 29, 30 and 31, or a soluble human CD39 fusion polypeptide comprising a leader containing sequence consisting of the amino acid sequence selected from the group consisting of a human IL-2 polypeptide of SEQ ID NO: 9, N-terminal amino acid sequence of human CD39L-1 consisting of Met 1 to Ser37 of SEQ ID NO: 31 or Ala residue fused to a human CD39 consisting of the amino acid sequence selected from the group consisting of amino acids 21-463 of SEQ ID NO: 30, Thr 38 to Thr 476 of SEQ ID NO: 2, and 49 to 487 of SEQ ID NO: 26. The specification on page 10 discloses that CD39 polypeptides comprise one to ten deletions, insertions, or substitutions of amino acid residues, when compared to a native CD39 sequence. Variants of CD39 include polypeptides that are naturally occurring such as allelic forms, spliced forms, as well as that have been modifying in the amino acid sequence of a CD39 polypeptide or polynucleotide such as polypeptides are at least about 70%, 80%, 90%, 95%, 98% and 99% identical to the native CD39 of SEQ ID NO: 2.

With the exception of the specific soluble human CD39 or fusion polypeptide mentioned above, there is insufficient written description about the structure associated with function of any and all CD39 polypeptide without the amino acid sequence. There is inadequate written description about the structure of the "heterologous peptide capable of adopting a stable secondary structure" in claim 1 without the amino acid sequence. In addition, the term "having" is open-ended. It expands the soluble CD39 such as polypeptide as set forth in claim 1(a), and any "fragments" thereof as set forth in claim 1(b) to include additional amino acids at either or both ends. There is a lack of written description as to which amino acids within the full length CD39 polypeptide to be added such that the resulting soluble CD39 polypeptide and variants thereof maintains its structure and biological activity. With regard to "fragments", there is a lack of written description about which amino acids within which "fragments" of 36 to 478 of SEQ ID NO: 2 to be deleted, added or modified such that the resulting soluble CD39 polypeptide fragments and variants thereof maintain its structure and apyrase activity. Further, the term "at least 70, 80, 90, 95, 98, 99 %" identical in amino acid sequence to a fragment of amino acids 36 to 478 of SEQ ID NO: 2 is ambiguous because the size of the fragment is unknown in claim 2. Even if the soluble CD39 polypeptide is limited to amino acids 36 to 478 of SEQ ID NO: 2, a polypeptide having a sequence "at least 70%, 80%, 90%, 95%, 98% and 99% identical to 36 to 478 of SEQ ID NO: 2 means 30%, 20%, 10%, 5%, 2% and 1% differences, respectively. In other words, the soluble CD39 polypeptide is equivalent to having at least 133, 88, 44, 22, 8 and 4 amino acids difference relative to 36 to 478 of SEQ ID NO: 2. There is insufficient disclosure as to which 133, 88, 44, 22, 8 and 4 amino acids relative to 36 to 478 of SEQ ID NO: 2 to be modified such as addition, deletion, substitution that the resulting polypeptide maintains its structure and function.

With regard to claim 4, the same reasons stated above apply to claim 4 in terms of "fragments" and "variants". Further, there is a lack of written disclosure as to the structure of "A" such as which 0-20 amino acids from the terminal portion of mature IL-2, "B" such as which linker peptide of 0-15 amino acids and Y such as soluble CD39 polypeptide without the amino acid sequence, let alone multiple "fragments" and "variants" of the undisclosed soluble CD39 polypeptide. The specification does not disclose any of the combination of amino terminus such as amino acids 36-44 and carboxyl terminus such as 471-478 of SEQ ID NO: 2 for the soluble CD39 polypeptide.

With regard to claim 5-7, the term "comprising" or "having" is open-ended. It expands the soluble CD39 polypeptide or fusion polypeptide to include additional amino acids at either or both ends in addition to the stated amino acids such as amino acids 25-464 of SEQ ID NO: 27; amino acids 25-464 of SEQ ID NO: 28; amino acids 27-473 of SEQ ID NO: 29, amino acids 21-476 of SEQ ID NO: 3; amino acids 21-476 of SEQ ID NO: 4; or amino acids 21-463 of SEQ ID NO: 30. There is inadequate written description about which amino acids to be added or which protein said SEQ ID NO fused to and whether the resulting soluble CD39 polypeptide or fusion polypeptide maintains its structure and function, in turn, would be useful for inhibiting platelet activation and treating disease such as stroke, or inhibiting angiogenesis. Given the unlimited number of CD39 polypeptide, fragments, variants thereof, it follows that any polypeptide having the structure of X-Y or A-B-Y has apyrase activity without the amino acid sequence is not adequately described. Since the structure of the polypeptides mentioned above are not adequately described, it follows that any polypeptide made by the process of culturing recombinant host cell such as COS cells is not adequately described. It also follows that any composition comprising any undisclosed polypeptide mentioned above and a pharmaceutically acceptable carrier are not adequately described.

Finally, the specification discloses only human CD39 polypeptide, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of CD39 or variants of CD39 to describe the genus for the claimed polypeptide. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 1-2, 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The plural "polypeptides" in claim 1(a), the plural "fragments of polypeptides" in claim 1(b) and the plural "variants of the polypeptides" in claim 1(c) do not match the singular "soluble CD39 polypeptide in claim 1, line 3.

The plural "polypeptides" in claim 2(a) and the plural "variant polypeptides" in claim 2(b) through (g) do not match the singular "soluble CD39 polypeptide in claim 2, line 1.

The plural "polypeptides" in claim 4(a), the plural "fragments of polypeptides" in claim 4(b) and the plural "variants of the polypeptides" in claim 4(c) do not match with the singular "soluble CD39 polypeptide in claim 4, lines 2-3.

The plural "fusion polypeptides" in claim 5(b) does not match the singular soluble CD39 polypeptide in claim 5, line 1.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 1-7 and 25-29 are rejected under 35 U.S.C. 102(a) as being anticipated by Gayle et al (J Clinical Investigation 101(9): 1851-1859, May 1998; PTO 1449) as evidence by Malizewski et al (J Immunol 153: 3574-3583, 1994; PTO 1449).

Gayle et al teach a polypeptide having a structure X-Y wherein X is a heterologous peptides capable of adopting a stable secondary structure such as the amino terminal or leader sequence of the mature IL-2 fused to Flag peptide of 10 amino acids and wherein Y is a soluble human CD39 comprising the human coding sequence from Thr 38 to Thr 476 identical to the claimed SEQ ID NO: 2 (see page 1852, col. 1, Expression plasmid construction, Figure 1, in particular) as evidence by Malizeqski et al (see page 3577 of J immunol, Figure 2 and Figure 7 of Malizeqski). The reference polypeptide comprising a soluble human CD39 (38-476) or the full length human CD39 inherently has apyrase activity (see Figure 1, solid domain, page 1851, col. 2, first full paragraph, in particular). Gayle et al further teach a polypeptide having the structure of A-B-Y wherein the reference A is the amino terminal portion of mature IL-2, B is a linker such as FLAG of 10 amino acids which is within the claimed linker of 0-15 amino acids and Y is soluble CD39 polypeptide having an amino acid sequence depicted in Figure 1 that has amino

acids Thr38 to Thr 476 of SEQ ID NO: 2 (see page 1852, col. 1, Expression plasmid construction, Fig. 1, in particular) as evidence by Malizeqski et al (see page 3577, Figure 2 of Malizeqski). Claims 5-7 are included in this rejection because the term "comprising" or "having" is open-ended. It expands the soluble polypeptide Thr 38 to Thr 476 of SEQ ID NO: 2 to include additional amino acids residues at either or both ends to include the reference full-length CD39. The reference polypeptide is produced by a process of preparing a soluble CD39 polypeptide comprising culturing a recombinant cell such as COS cell or CHO cell under condition to permit expression of the reference CD39 polypeptide and recovering the reference polypeptide from the culture (see Methods on page 1852, col. 1, in particular). The reference CHO cell has been adapted to grow in suspension in the absence of serum (see page 1852, col. 1, paragraph "Development of a stably transfected cell line secreting solCD39", in particular). Gayle et al teach a composition comprising the reference polypeptide such as soluble CD39 and a pharmaceutically acceptable carrier such as sodium phosphate or PBS or Hepes (see page 1852, col. 2, first full paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

14. Claims 1-2, 5-7, and 25-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Malizewski et al (J Immunol 153: 3574-3583, 1994; PTO 1449).

Malizewski et al teach various soluble CD39 polypeptide having a structure of X-Y wherein the X is a heterologous peptide such as human IgG1 Fc domain linked to a soluble human or mouse CD39 polypeptide (see Figure 9 legend, page 3581, col. 2, second full paragraph, in particular). The reference heterologous peptide inherently capable of adopting a stable secondary structure. Malizewski et al teach various soluble polypeptide comprising human CD39-Fc and murine CD39-Fc (see Figure 9, in particular). The reference full length human soluble CD39 is 100% identical to the full length polypeptide of claimed SEQ ID NO: 2 (see Figure 7, amino acid sequence of human CD39, in particular) which is at least 70%, 80%, 90%, 95%, 98% and 99% identical to the amino acid sequence to claimed amino acids 36 to 478 of SEQ ID NO: 2. The reference soluble human CD39 inherently comprises amino acid residues of the claimed 21-463 of SEQ ID NO: 30 (see Figure 9 legend, page 3581, col. 2, second full paragraph, in particular). The term "comprising" or "having" is open-ended. It expands the claimed 21-463 of SEQ ID NO: 3 to include additional amino acids at either or both ends to include the reference fusion or soluble human CD39 polypeptide. The reference soluble CD39

polypeptide is also a fusion polypeptide since the C terminal hydrophobic region of the human CD39 polypeptide is replaced with the human IgG1 Fc domain (see page 3581, col. 2, par. 2, in particular). Malizewski et al also teach variants of human CD39 such as murine CD39 (see figure 7, in particular). The reference human or murine soluble CD39 polypeptide is produced by culturing a recombinant host cell such as COS cell transfected with the cDNA encoding the full-length human or murine CD39-Fc (see Figure 8 legend, in particular) and the reference CHO cell has been adapted to grow in suspension and in the absence of serum (see page 3575, col. 1, cDNA expression and immunoselection, in particular). Malizewski et al further teaches a composition comprising a pharmaceutically acceptable carrier such as PBS and the reference polypeptide (see page 3575, col. 2, Immunoprecipitation and SDS-PAGE, in particular). Thus, the reference teachings anticipate the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malizewski et al (J Immunol 153: 3574-3583, 1994; PTO 1449) in view of Cullen et al (DNA 7(9): 645-650, 1988; PTO 1449).

The teachings of Malizewski et al have been discussed supra.

The claimed invention in claim 3 differs from the teachings of the reference only in that the polypeptide wherein X is peptide fragment from the amino terminal portion of mature IL-2.

The claimed invention in claim 4 differs from the teachings of the reference only in that the polypeptide having a structure A-B-Y wherein A is 5-10 amino acids from the amino terminal portion of mature IL-2, B is a linker of 1 amino acid and Y is soluble CD39 polypeptide.

Cullen et al teach leader peptide such as IL-2 amino terminal fragment of IL-2 of five to ten amino acids in length or rat preproinsulin II operably linked to the N-terminus of any polypeptide such as IL-2 via an amino acid linker (see abstract, Fig 1, page 648, col. 1, first full paragraph, in particular). The heterologous leader peptide significantly enhances the secretion of the desired polypeptide (see page 645, col. 2, first full paragraph, page 648, col. 1, first and second paragraph, Table 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the leader peptide in amino terminal portion of CD39 polypeptide as taught by Malizewski et al for the heterologous leader peptide such as leader peptide from the amino terminal portion of mature IL-2 as taught by Cullen et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because heterologous leader peptide significantly enhances the secretion of the desired polypeptide as taught by Cullen et al (see page 645, col. 2, first full paragraph).

18. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malizewski et al (J Immunol 153: 3574-3583, 1994; PTO 1449) in view of Cullen et al (DNA 7(9): 645-650, 1988; PTO 1449) and US Pat No 6,476,211 (Filed July 16, 1998; PTO 892).

The teachings of Malizewski et al have been discussed supra.

The claimed invention in claim 3 differs from the teachings of the reference only in that the polypeptide wherein X is peptide fragment from the amino terminal portion of mature CD39-L2, CD39-L3 or CD39-L4.

Cullen et al teach leader peptide such as IL-2 amino terminal fragment of IL-2 of five to ten amino acids in length or rat preproinsulin II operably linked to the N-terminus of any polypeptide such as IL-2 via an amino acid linker (see abstract, Fig 1, page 648, col. 1, first full paragraph, in particular). The heterologous leader peptide significantly enhances the secretion of the desired polypeptide (see page 645, col. 2, first full paragraph, page 648, col. 1, first and second paragraph, Table 1, in particular).

The '211 patent teaches various mature CD39L-2 (SEQ ID NO: 27) and CD39-4 (SEQ ID NO: 3) (see col. 4, line 25-30, in particular). The reference CD39-L2 and CD39-L4 are related to human CD39 that has ATPDase (see col. 1, line 34-67, col. 3, lines 29-30, in particular). The '211 patent teaches where desired, an expression vector may be designed to contain a "signal or leader sequence" which will direct the polypeptide through the membrane of a cell (see col. 12, lines 32-45, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the leader peptide in amino terminal portion of CD39 polypeptide as taught by Malizewski et al for the heterologous leader peptide such as leader peptide from the amino terminal portion of mature CD39-L2 or CD39-L4 as taught by the '211 patent for enhances the expression of the desired polypeptide as taught by Cullen et al and the '211 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because heterologous leader peptide significantly enhances the secretion of the desired polypeptide as taught by Cullen et al (see page 645, col. 2, first full paragraph). The '211 patent teaches where desired, an expression vector may be designed to contain a "signal or leader sequence" which will direct the polypeptide through the membrane of a cell (see col. 12, lines 32-45, in particular).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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